Independent at heart: persistent association of altitude with ischaemic heart disease mortality after consideration of climate, topography and built environment

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Abstract: BACKGROUND: Living at higher altitude was dose-dependently associated with lower risk of ischaemic heart disease (IHD). Higher altitudes have different climatic, topographic and built environment properties than lowland regions. It is unclear whether these environmental factors mediate/confound the association between altitude and IHD. We examined how much of the altitude-IHD association is explained by variations in exposure at place of residence to sunshine, temperature, precipitation, aspect, slope and distance to main road. METHODS: We included 4.2 million individuals aged 40-84 at baseline living in Switzerland at altitudes 195-2971 m above sea level (ie, full range of residence), providing 77 127 IHD deaths. Mortality data 2000-2008, sociodemographic/economic information and coordinates of residence were obtained from the Swiss National Cohort, a longitudinal, census-based record linkage study. Environment information was modelled to residence level using Weibull regression models. RESULTS: In the model not adjusted for other environmental factors, IHD mortality linearly decreased with increasing altitude resulting in a lower risk (HR, 95% CI 0.67, 0.60 to 0.74) for those living >1500 m (vs<600 m). This association remained after adjustment for all other environmental factors 0.74 (0.66 to 0.82). CONCLUSIONS: The benefit of living at higher altitude was only partially confounded by variations in climate, topography and built environment. Rather, physical environment factors appear to have an independent effect and may impact on cardiovascular health in a cumulative way. Inclusion of additional modifiable factors as well as individual information on traditional IHD risk factors in our combined environmental model could help to identify strategies for the reduction of inequalities in IHD mortality.

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Independent at heart: Persistent association of altitude with ischemic heart disease mortality after consideration of climate, topography and built environment - a longitudinal cohort study

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Key words Ischemic heart disease; physical environment; topography; climate; moderate altitude

ABSTRACT

Background Living at higher altitude was dose-dependently associated with lower risk of ischemic heart disease (IHD). Higher altitudes have different climatic, topographic and built environment properties than lowland regions. It is unclear whether these environmental factors mediate/confound the association between altitude and IHD. We examined how much of the altitude-IHD association is explained by variations in exposure at place of residence to sunshine, temperature, precipitation, aspect, slope and distance to main road.

Methods We included 4.2 million individuals aged 40-84 at baseline living in Switzerland at altitudes 195-2971m above sea level (i.e. full range of residence), providing 77,127 ischemic heart disease deaths. Mortality data 2000-2008, sociodemographic/economic information and coordinates of residence were obtained from the Swiss National Cohort, a longitudinal, census-based record linkage study. Environment information was modelled to residence level. Risks were calculated with Weibull regression.

Results In the model not adjusted for other environmental factors, IHD mortality linearly decreased with increasing altitude resulting in a lower risk (Hazard Ratio, 95% confidence interval: 0.67, 0.60-0.74) for those living >1500m (vs<600m). This association remained after adjustment for all other environmental factors 0.74 (0.66-0.82).

Conclusions The benefit of living at higher altitude was only partially confounded by variations in climate, topography and built environment. Rather, physical environment factors appear to have an independent effect and may impact on cardiovascular health in a cumulative way. Inclusion of additional modifiable factors as well as individual information on traditional IHD risk factors in our combined environmental model could help to identify strategies for the reduction of inequalities in IHD mortality.

INTRODUCTION

An individual's physical environment has a marked and sustained impact on its cardiovascular health. Either directly via climatic conditions or stressors from the built environment such as air pollution and noise or indirectly by influencing the individuals behavior and its impact on health, e.g. the opportunities for and the impact of leisure time physical activity and active commuting (1–5). We previously showed that ischemic heart disease mortality (IHD) was inversely and "dose-dependently" associated with altitude in the general adult population of German Switzerland (6). Environmental factors are not independent from each other such as sunshine duration, ambient temperature, and precipitation, but also terrain slope, geographical aspect and infrastructure may go along with altitude. In fact, the potential protective effect of altitude on IHD may not directly be linked to altitude itself but rather be confounded by factors differing between high- and lowland regions (6). In Switzerland, regions situated at higher altitudes generally have a more sunny and dry climate and less pollution. Others showed that these factors are independently associated with IHD mortality and it is possible that not altitude per se but other (environmental) factors are responsible for the lower mortality risk previously reported (4). However, worldwide only few settings allow to properly disentangle the impact of individual exposure to climatic, topographical, and man-made environmental factors on cardiovascular health. Switzerland offers a unique framework for such analyses because it has a large variation in a broad range of environmental parameters within a small area, but only negligible geographical differences in access to and quality of health care and in ethnicity (6,7). Thanks to the combination of different sources providing individual data, the association between environment and health outcomes can be studied on the individuals' building-of-residence level (8,9).
In this study, we examined whether the inverse altitude-IHD association previously found is confounded by related environmental factors or whether altitude exerts an independent effect on cardiovascular health (6). To the best of our knowledge, this is the first study using person data from a virtually complete general adult population and considering a wide range of environmental factors that cover residential circumstances. Based on our previous analyses and speculations(6), we hypothesize that the altitude-IHD mortality association substantially weakens or disappears after consideration of climatic, terrain and infrastructure factors.

METHODS

Study population

The Swiss National Cohort, described in detail elsewhere (10,11), is a nationwide longitudinal research platform based on individual data collected by the Swiss Federal Statistical Office. In short, individual records of 1990 and 2000 census were linked using probabilistic record linkage methods (10,11). In Switzerland, the participation in the census is mandatory (12). Non-participation is considered to be negligible (coverage of 98.6% for the 2000 census)(13). Record linkage was based on variables, which were available at both censuses, e.g. date of birth, sex, marital status, nationality, religion, place of residence and date of birth of partner and children. Further, individual records of the Swiss mortality registry were linked, leading to a database with 7,280,246 (2000 census) individuals. Due to small numbers of IHD deaths at younger ages and the uncertainty of assignment of cause of death at oldest age, we limited age to 40-85 years. The study population consisted of all residents in Switzerland at 2000 census (5th December 2000) with follow-up time till end of 2008, date of emigration, date of death, or 85th birthday, whatever occurred first. Persons were excluded if they were younger than 40 at the 2000 census or did not turn 40 during the observation time (n=2,830,230), were 85 or older at the census (n=144,043), died on the date of the census (n=215) or had no geocoded place of residence (n=147,038).

Variables and definitions

Socio-demographic variables from the Swiss National Cohort were based on individual records, like gender, marital status (single, married, widowed, divorced), educational level (compulsory and missing/unknown education, secondary and tertiary), socio-professional attainment (management, self-employed, professionals, skilled labor, unskilled employees, not in paid employment, unemployed, and others), household type (single person, multi person and institution), language region (German, French, Italian) and an area-based index of socio-economic position (Swiss-SEP) (8), in deciles. The Swiss-SEP is based on neighbourhoods of 50 households with overlapping boundaries that were defined using census and road network data. It combines median rent per square metre,

proportion households headed by a person with primary education or less, proportion headed by a person in manual or unskilled occupation and the mean number of persons per room. The Swiss-SEP considers both individual and area information by additionally taking into account an individual's neighbourhood socioeconomic context. Thus, the Swiss-SEP also includes a "contextual" element, in contrast to purely "compositional" SEP-variables (14). We included language region in order to account for cultural diversity which are independent of environmental factors. Differences in diet (particularly "risk reducing" alcohol consumption patterns) are likely contributing to variations in IHD-mortality between language regions (15).
In order to obtain precise altitude for each dwelling building, we used SwissALTI3D (16). This is a digital elevation model which describes the topography of Switzerland with a precision of 1-3m. We overlaid the Swiss coordinates of buildings at 2000 census to assign the altitude above sea-level in meters (full range: 195-2971m). Altitude of each building was categorized into <600m, 600-<900m, 900-<1200m, 1200-<1500m, ≥1500m.

Environmental variables were modeled on the building level. Using SwissALTI3D, we derived the terrain slope at place of residence (<3%, 3-<5%, 5-<10%, 10-<15%, 15-<25%, >=25%) using a 20x20m raster as well as geographical aspect (no aspect, N, NE, E, SE, S, SW, W, WE). We included this because aspect (azimuth) is partially responsible for climatic variations (in particular the effective sunshine duration) between regions north (mainly German speaking part of Switzerland) and south of the Alps (mainly Italian speaking part). Communes of the south of the Alps are more likely "aligned towards the sun" while otherwise analogue communes of the north of the Alps morel likely are "in the shadow of a mountain". Aspect could therewith also influence variations in IHD mortality between the two language regions or within a valley, by "modulating" climatic conditions. Aspect could also play a role within smaller scale areas such as valleys with some buildings lying on the "dark" or the "sunny" side of the valley. No aspect was assigned to buildings with slope <3%. Distance to main road (<50m, 50-<100m, 100-<150m, 150-<200m >=200m) was used as a proxy for traffic related air pollution and noise exposure. This distance was correlated with traffic exposure and can be (relatively) validly used as surrogate (17). Since in Switzerland all large cities are situated on lower altitudes, we considered a dummy variable for urbanisation (values: urban, peri-urban, rural). Mountain area was defined according to Schuler et al (18). From MeteoSwiss (19), we used modeled climate data, derived from stations with an average distance of approximately 20-30km, to calculate annual means (1981-85) for precipitation, temperature, and proportion of maximal possible sunshine duration. To evaluate the effect of moving to a place with different altitude between place of birth and 2000 census, we included a variable with 1) altitude at place of residence 2000 equal to altitude at place of birth (=reference), +/-400m; 2) altitude at census >+400m and 3) altitude at census <-400m, compared to altitude at place of birth.

Outcome
Causes of death were coded according to the 10th revision of the International Classification of Diseases, Injures and Causes of Death (ICD-10). The outcome of interest was IHD (ICD-10 I20-I25).

Statistical analysis
Correlations between variables were obtained with Pearson’s correlation coefficients. Mortality hazard ratios (HR) and 95% confidence intervals (CIs) were calculated using Weibull proportional hazards regression models. In order to assess possible bias due to model distributional misspecification, we used Cox survival regression models as a sensitivity analysis (20). The proportional hazard assumption has been tested by Schoenfeld residuals. Time of observation started on December 5th 2000 (date of 2000 census) and ended on the date of death, emigration or December 31st 2008, whatever occurred first. The underlying time-scale was observation time. All models were adjusted for continuous age, modeled as restricted cubic splines using five predefined knots based on percentiles(21). To avoid collinearity, our statistical software automatically avoided the simultaneous use of aspect and slope in the same model. We therefore used them in separate models. No other collinearity precluding analyses was detected by the software.
In supplementary analyses we, a) modeled altitude as restricted cubic splines, with median altitude as the reference, b) restricted the study population to people living in the mountain area, c) analyzed the

data for people living <600m separately and d) evaluated changes in altitude at place of birth vs. residence at census. Analyses were performed with Stata 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX).

RESULTS

Descriptive

Figure 1 shows the distribution of the population and the environmental variables over the country. The figures suggest that the distribution of the variables is associated with altitude with higher density of residential buildings but lower slope and less sunshine at lower altitudes. Population and road density go along with that of the buildings (Figure A1 and A2). Mean annual precipitations do only partially follow the patterns of altitude and sunshine duration. Inhabited highland regions (>1200m) have relatively few precipitations but regions in-between (900-1200m) have more precipitation than lowland regions (<600m). A combination of high mean precipitation and sunshine duration as well as sloped terrain and relatively low altitude can be observed in the southeastern Italian speaking part of Switzerland. In contrast, in the northern part of the country, a combination of low altitude, less sunshine and low precipitation exists. Correlation between environmental variables are shown in Table A1. Altitude was positively associated with sunshine duration, precipitation, slope, distance to main road and negatively with temperature.
Table 1 describes the population and its distribution over the altitudinal ranges and by category of the selected environmental variables.

Table 1 Number and percentage of Swiss residents by environmental factors and altitude range of the place or residence, Swiss National Cohort 2000-2008

Altitude range in m above sea level (census 2000)	<600		600-<900		900-<1200		1200-<1500		≥1500		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Population (40-84y)	3 321 321	80	624 519	15	139 802	3	43 561	1	29 517	1	4 158 720	100
Deaths (IHD)	61 367	80	11 727	15	2 895	4	780	1	358	0	77 127	100
Gender												
Men	1 597 523	48	305 026	49	68 533	49	21 465	49	14 758	50	2 007 305	48
Women	1 723 798	52	319 493	51	71 269	51	22 096	51	14 759	50	2 151 415	52
Sunshine duration in % of maximum												
32.6 - 34.9	767 502	23	69 407	11	604	0	18	0	0	0	837 531	20
35.0 - 35.7	745 938	23	82 015	13	674	1	18	0	0	0	828 645	20
35.8 - 37.7	687 171	21	135 041	22	11 799	8	187	0	13	0	834 211	20
37.8 - 41.0	593 822	18	206 869	33	48 219	35	371	1	24	0	849 305	20
41.1 - 58.5	526 888	16	131 187	21	78 506	56	42 967	99	2 948	100	809 028	20
Precipitation in mm												
540 - 993	753 601	23	42 608	7	13 637	10	13 418	31	19 852	67	843 116	20
994 - 1080	795 061	24	20 647	3	6 291	5	3 614	8	3 859	13	829 472	20
1081 - 1165	757 813	23	55 199	9	4 074	3	6 086	14	1 134	4	824 306	20
1166 - 1316	583 182	18	233 692	37	7 221	5	7 113	16	1 682	6	832 890	20
1317 - 2735	431 664	13	272 373	44	108 579	78	1 333	31	299	10	828 936	20
Temperature in degree C												
-3.8 - 7.9	203 298	6	419 940	67	134 903	97	42 597	98	29 517	100	830 255	20
8.0 - 8.5	702 176	21	127 019	20	3 212	2	642	2	0	0	833 049	20
8.6 - 8.7	800 097	24	36 141	6	804	1	174	0	0	0	837 216	20
8.8 - 9.4	793 210	24	33 660	5	699	1	134	0	0	0	827 703	20
9.5 - 12.5	822 540	25	7 759	1	184	0	14	0	0	0	830 497	20
Slope at place of residence in %												
0 - <3 (flat)	1 361 191	41	163 107	26	24 637	18	4 003	9	5 455	19	1 558 393	38
3 - <5	61 112	18	101 318	16	18 861	14	3 493	8	3 457	12	738 249	18
5 - <10	82 888	25	183 911	29	40 923	29	1 158	27	7 629	26	1 072 923	26
10 - <15	348 574	11	113 665	18	3 124	22	12 345	28	6 064	21	511 888	12
15 - <25	141 636	4	52 863	9	19 772	14	9 986	23	5 174	18	229 431	6
≥25	2 992	1	9 655	2	4 369	3	2 154	5	1 738	6	47 836	1
Geographical aspect in cardinal direction												
No aspect, flat	1 361 191	41	163 107	26	24 637	17	4 003	9	5 455	18	1 558 393	37
N	75 444	2	19 901	3	2 667	2	938	2	270	1	99 220	2
NE	278 194	8	51 351	8	7 934	6	2 764	7	1 625	6	341 868	8
E	283 304	9	56 370	9	13 036	9	4 765	11	3 980	13	361 455	9
SE	278 558	8	77 233	13	28 975	21	9 016	21	6 111	21	399 893	10
S	286 105	9	74 288	12	23 727	17	8 340	19	4 168	14	396 628	10
SW	278 542	8	62 998	10	14 135	10	6 215	14	3 231	11	365 121	9
W	249 106	8	57 167	9	12 079	9	4 482	10	2 751	9	325 585	8
NW	230 877	7	62 104	10	12 612	9	3 038	7	1 926	7	310 557	7
Distance to main road in m												
0 - <50	404 151	12	68 792	11	20 672	15	5 782	13	2 932	10	502 329	12
50 - <100	370 272	11	55 024	9	12 921	9	3 174	7	2 239	8	44 363	11
100 - <150	31 293	9	45 019	7	8 247	6	2 021	5	2 000	7	370 217	9
150 - <200	269 393	8	36 474	6	6 368	5	1 171	3	1 374	5	31 478	8
≥200	1 964 575	59	41 921	67	91 594	66	31 413	72	20 972	71	2 527 764	61

Socio-economic/demographic factors are shown in Table A2, supplementary files

Socio-demographic factors are shown in Table A2. At baseline, 4,158,720 individuals were included, of whom 77,127 died of IHD during the observation time. Person-years amounted to 27.8 million. Because all large cities are in lower areas, 80% of Swiss residents live at altitudes <600m. With increasing altitude, the quintiles of sunshine duration and precipitation are increasingly unevenly distributed with a trend to more sunshine and less rain/snow at higher altitudes. Above 1500m, the mean annual temperatures were below 8 degrees Celsius. Expectedly, the proportion of flat terrain decreases with increasing altitude. However, the lowest proportion of flat landscape (slope <5%: 17%) is found at altitudes 1200-<1500m. This is due to the fact that altitudes >1500m mainly stem from one high-lying wide valley (Engadin) situated in the south-eastern part of the country with a large proportion of flat terrain (slope <5%: 31%). In contrast, distances of the residence building to a main road do not vary much over altitudinal belts.

Multivariable analysis
Figure 2 shows the risk of death from IHD relative to the altitude, continuously modeled as restricted cubic splines. The hazards of IHD mortality are shown to the reference of the median altitude of all residents in the study population (473m) for the 0.1-99.9 percentile of altitude (199-1804m). Below the median altitude, the relative risk remains unchanged, while it linearly decreases with increasing altitude. Analysis over the full range of altitude shows the same pattern (Figure A3). Results from adjusted models are shown in Table 2 (those of the socioeconomic/demographic variables in Table A3). Results from a sensitivity analysis based on Cox regression were very similar.

Table 2 Hazard ratios for ischemic heart disease mortality of Swiss residents (aged 40-84 years) from models with increasing adjustment, Swiss National Cohort 2000-2008 (n=4,158,720)

	Crude Model[a]	**Model 1**[b]	**Model 2**[c]	**Model 3**[c]	**Model 4**[c]	**Model 5**[c]	**Model 6**[c]	**Model 7**[c]
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Altitude range in m above sea level (census 2000)								
<600	1	1	1	1	1	1	1	1
600-<900	1.01 (0.99-1.03)	0.98 (0.95-1.00)	0.97 (0.94-0.99)	0.98 (0.96-1.00)	0.98 (0.96-1.00)	0.98 (0.96-1.00)	0.97 (0.95-1.00)	0.97 (0.94-1.00)
900-<1200	0.96 (0.93-1.00)	0.96 (0.92-1.00)	0.96 (0.92-1.01)	0.97 (0.93-1.01)	0.96 (0.92-1.00)	0.96 (0.93-1.00)	0.97 (0.93-1.02)	0.96 (0.92-1.01)
1200-<1500	0.85 (0.80-0.92)	0.78 (0.72-0.83)	0.82 (0.76-0.88)	0.79 (0.73-0.85)	0.78 (0.72-0.84)	0.78 (0.72-0.84)	0.83 (0.77-0.90)	0.82 (0.76-0.89)
≥1500	0.75 (0.68-0.83)	0.67 (0.60-0.74)	0.73 (0.65-0.81)	0.68 (0.61-0.75)	0.67 (0.60-0.74)	0.67 (0.60-0.74)	0.74 (0.66-0.82)	0.73 (0.65-0.81)
Mean annual sunshine duration in % of maximum								
32.6 - <35.0	1		1				1	1
35.0 - <35.8	1.02 (1.00-1.04)		1.05 (1.03-1.07)				1.05 (1.02-1.07)	1.05 (1.03-1.07)
35.8 - <37.6	0.95 (0.93-0.97)		1.02 (1.00-1.05)				1.02 (1.00-1.05)	1.02 (1.00-1.05)
37.6 - <41.4	0.76 (0.74-0.78)		0.94 (0.92-0.97)				0.94 (0.92-0.97)	0.94 (0.92-0.97)
41.4 - 58.5	0.85 (0.83-0.87)		0.94 (0.91-0.96)				0.94 (0.91-0.97)	0.94 (0.91-0.97)
Mean annual precipitation in mm								
540 - 993	1		1				1	1
994 - 1080	1.09 (1.07-1.12)		1.03 (1.00-1.05)				1.03 (1.00-1.05)	1.03 (1.00-1.05)
1081 - 1165	1.13 (1.10-1.15)		1.05 (1.03-1.08)				1.06 (1.03-1.08)	1.06 (1.03-1.08)
1166 - 1316	1.10 (1.08-1.13)		1.04 (1.01-1.07)				1.04 (1.01-1.07)	1.04 (1.01-1.07)
1317 - 2735	1.11 (1.09-1.14)		1.09 (1.06-1.12)				1.09 (1.06-1.12)	1.09 (1.06-1.12)
Mean annual temperature in degree C								
-3.3-<8.6	1		1				1	1
8.6-<9.2	1.02 (1.00-1.04)		1.01 (0.98-1.03)				1.01 (0.98-1.03)	1.01 (0.98-1.03)
9.2-<9.6	1.05 (1.03-1.07)		1.02 (0.99-1.05)				1.02 (0.99-1.06)	1.02 (0.99-1.06)
9.6-<10.0	1.00 (0.98-1.02)		0.98 (0.95-1.01)				0.98 (0.95-1.01)	0.98 (0.95-1.01)
10.0-<13.4	0.78 (0.77-0.80)		0.96 (0.93-1.00)				0.96 (0.92-0.99)	0.96 (0.92-0.99)
Slope at place of residence in %								
0 - <3 (flat)	1			1			1	
3 - <5	1.00 (0.98-1.02)			1.00 (0.98-1.02)			1.00 (0.98-1.02)	
5 - <10	0.98 (0.96-1.00)			1.00 (0.98-1.02)			0.99 (0.97-1.01)	
10 - <15	0.94 (0.92-0.96)			0.96 (0.94-0.99)			0.96 (0.94-0.98)	
15 - <25	0.92 (0.89-0.95)			0.96 (0.93-0.99)			0.96 (0.93-0.99)	
≥25	0.86 (0.80-0.92)			0.92 (0.86-0.99)			0.92 (0.85-0.99)	
Geographical aspect in cardinal direction[d]								
None: flat	1				1			1
N	0.99 (0.95-1.04)				0.96 (0.91-1.01)			0.95 (0.91-1.00)

NE	1.01 (0.99-1.04)				0.99 (0.97-1.02)			0.99 (0.96-1.02)
E	0.97 (0.95-1.00)				0.98 (0.96-1.01)			0.98 (0.95-1.00)
SE	0.96 (0.93-0.98)				1.01 (0.98-1.03)			1.00 (0.97-1.03)
S	0.95 (0.93-0.98)				1.00 (0.97-1.02)			0.99 (0.97-1.02)
SW	0.93 (0.91-0.96)				0.97 (0.95-1.00)			0.97 (0.94-0.99)
W	0.97 (0.95-1.00)				0.99 (0.96-1.02)			0.99 (0.96-1.01)
NW	1.00 (0.97-1.03)				0.99 (0.96-1.02)			0.98 (0.96-1.01)
Distance to main road in m								
0 - <50	1					1	1	1
50 - <100	0.96 (0.93-0.99)					0.97 (0.94-1.00)	0.97 (0.94-1.00)	0.97 (0.94-1.00)
100 - <150	0.94 (0.91-0.97)					0.95 (0.92-0.98)	0.95 (0.92-0.98)	0.95 (0.92-0.98)
150 - <200	0.92 (0.89-0.95)					0.93 (0.90-0.96)	0.93 (0.90-0.96)	0.93 (0.90-0.96)
≥200	0.94 (0.92-0.96)					0.92 (0.90-0.95)	0.92 (0.90-0.94)	0.92 (0.90-0.94)

[a]each variable adjusted for age
[b]adjusted for age, sex, marital status, education, profession, type of household, language region, urbanisation and Swiss SEP (see Table A3)
[c]adjusted for age, sex, marital status, education, profession, type of household, language region, urbanisation, Swiss SEP (see Table A3) and variables listed in column (i.e., Model 2 was adjusted for the meteorological variables sunshine, precipitation, temperature but not for slope/aspect, road distance)
[d]to avoid collinearity, slope (Model 6) and aspect (Model 7) were not simultaneously included in models
Socio-economic/demographic factors are shown in Table A3, supplementary files

Results were similar in men and women and the sex-interaction term was not significant (Model 7 p=0.22). The environmental variables were positively (altitude, sunshine, slope, road distance) or inversely (precipitation) associated with IHD mortality (Crude Model). In the fully adjusted model, IHD mortality was lower in the top quintile of temperature whereas there was no statistically significant association with aspect. The association between higher altitude and lower risk of death of IHD strengthened after adjustment for socio-demographic/economic factors (Model 1). The associations of these variables with IHD mortality and the number of people in the respective categories are shown in Table A2 and A3, respectively. After further adjustment for sunshine, precipitation and temperature (Model 2), slope (Model 3), aspect (Model 4), road distance (Model 5), and the combined models (6+7), the association between higher altitude and lower IHD mortality remained stable and statistically significant. Moreover, even after full adjustment (Models 6+7), most environmental variables remained associated with IHD mortality, meaning that their impact on risk of death of IHD was (at least partially) independent from each other. This was also the case when looking only at altitudes <600m (Table A4) and, for some variables, also only in the mountain area (Table A5). These results need to be interpreted cautiously due to the strongly reduced variation in the data. Inclusion of information of altitude at place of birth had an impact on the association of IHD with environmental factors. Compared to those who did not move (altitude at place of birth = altitude (+/-) at place of residence), people who moved down to lower altitudes had a lower risk, whereas those who moved up adapted their risk according to the corresponding altitude (Table A6). However, for about one third of the total population, information on place of birth was not available or not utilizable (e.g. because place of birth was abroad).

DISCUSSION

Main results

Based on the virtually complete adult population of Switzerland, we explored whether the association between living at moderately higher altitude and having a lower risk of IHD was confounded by variations in climate, terrain properties and built environment. We found that the inverse altitude-IHD association remained after consideration of all other environmental factors. In the final fully adjusted model, most of the latter were still associated with IHD mortality suggesting a partially independent role of considered environmental factors.

Comparison with other studies

Few studies have looked at the association between altitude and IHD. Their results had limited generalizability because of small or selected population samples and/or because of their study design (3,22–25). To the best of our knowledge, only two studies adjusted the altitude-IHD relationship for environmental measures, however for one factor only. In line with our results, this association remained significant after adjustment for background radiation and solar radiation respectively (3,22). In our fully adjusted model, most of the environmental variables remained associated with IHD. This is partially at odds with a study conducted in England showing that in a joint model, sunshine and temperature but not air pollution remained (inversely) associated with IHD (4). Similarly to our results, others found that the inverse association of altitude with stroke and all-cause mortality was weaker compared to that with IHD (22,23,25).

Possible mechanisms

In our study, the potentially protective effect of living at higher altitude on IHD was not substantially blunted by parameters which are (partially) associated with altitude: climatic properties, topography, and factors related to road infrastructure . In accordance with others, our results suggest a more direct protective effect on cardiovascular health via the decrease in oxygen partial pressure with increasing altitude (3,26). The long-term physiological and anatomical adaptations to this affect the circulatory system, the heart, the blood and the autonomic nervous system (5,27–34). Favorable changes associated with exposure to moderate altitude were also reported regarding lipid metabolism and blood pressure (35,36). The adaptations in erythrocytes were such that oxygen carrying capacity and the release at the tissue level were increased (27,31). High-altitude residents also showed an enhanced vagal tone and a reduced tendency for vasoconstriction compared to sea-level resides (30,31).

Several heart-specific adaptations occurring after long-term exposure to moderate altitude could explain why we observed a stronger and more linear effect for IHD than for stroke. The myocardium of mountaineers has an increased oxygen extraction, an improved mitochondrial energy efficiency and a preference to metabolize glucose over free fatty acids (31,32). Relative hypoxemia also stimulates myocardial angiogenesis and arterial and ventricular remodeling and enhances the contractile functional reserve of the myocardium (28,29,33). Likely, these adaptations already occur at moderate altitudes (27,34). Many of the physiological adaptations are specific to the heart which could explain that the association of environmental exposures were stronger for IHD than for stroke (5,6). The fact that Swiss highlanders who have been born at higher altitude "preserve" their lower IHD risk when they migrate to lower altitudes, suggests that these adaptations are at least partially sustainable. This supports the biological plausibility of a causal impact of circumstances prevailing at higher altitudes on myocardium and circulation (6). Genetic adaptation to high altitude has been reported (37). It is however very unlikely, that such adaptation played a role in our population because there is substantial migration between regions of different altitudes (6).

Strengths and Limitations

Our study is unique in the sense that it includes individual data from a very large and almost complete population with detailed and specific information on wide range of environmental exposures. In contrast to other studies, we were able to model exposures not only on the level of commune but on a finer residence building level. In combination with the availability of various potential confounders and the large number of IHD cases, this allowed robust and valid analyses. Other strong points of this study are the lack of relevant ethnic differences between high- and lowlanders and the fact that the study population was distributed over virtually all altitudes allowing to examine the association dose-dependently. The impact of cultural variations in assignment of cause of death is expected to be small and could be adjusted for in the models by consideration of language region.

Our study was limited by the fact that we were not able to adjust for behavioural and clinical risk factors like smoking, physical activity, obesity or high blood pressure. However, as shown previously (38,39), these factors are strongly associated with socio-economic position which we have considered in our analyses with several variables. We also found no variations in lung cancer mortality (not shown) and much smaller variations in stroke mortality by altitude. These causes of death have common risk factors (i.e. smoking and hypertension) with IHD and one would expect lower HRs for lung cancer and stroke at higher altitude if highlanders smoked less often than lowlanders. As previously shown with separate survey data, there were indeed no statistically significant differences by altitude in traditional CVD risk factors. We would therefore not expect a major impact on the altitude-mortality association of the inclusion of these risk factors in our model. However, it would be crucial to obtain individual information on potential intermediate factors e.g., blood pressure, lipids, sugar, in order to better elucidate prevention pathways driven by altitude. Therefore, we would not expect a substantial impact on results with inclusion of other risk factors all the more because we found no evidence for differences by altitude based on survey data (6). We used distance to main road as a proxy for exposure to noise, artificial light and air pollution. High resolution 3D models of air pollution and noise, which are not available yet, could better account for traffic associated exposure. We cannot exclude that a rural-urban effect contributed to variations in IHD-mortality, even though we adjusted for urbanisation. However, several findings speak against such an effect. IHD-mortality was higher in rural and peri-urban than in urban regions (Table A3). Moreover, risk patterns and gradients remain the same when limiting to regions <600m or to mountain areas (Table A4 and Table A5). Lower IHD mortality in urban regions also do not support the assumption that heart patients living at higher altitudes move to larger cities once they become ill. Unfortunately we only had crude and limited information on migration of individuals across environmental factors. Novel data collection approaches of the Swiss National Cohort will allow to better follow people's changes in residence over life course. We were limited to mortality as outcome. Altitude may have a different impact on incident disease not immediately leading to death (5). We cannot exclude that the altitude-IHD-association was (partially) due to residual confounding.

CONCLUSION

Lower mortality from IHD at higher altitude cannot be attributed to factors that are associated with altitude: climate, topography, and factors related to road infrastructure. Rather, these environmental factors may independently influence cardiovascular health. This opens door for further analyses allowing to prioritize modifiable environmental factors regarding their potential impact on health. Consideration of additional, more specific modifiable factors e.g., noise and air pollution, land use and building type, would allow to establish an information basis enabling city and infrastructure planners and public health authorities to create more friendly environments and to reduce ambient-related health inequalities.

What is already known on this subject
Living at higher altitude is inversely associated with ischemic heart disease (IHD) mortality. Higher altitudes have different climatic, topographic and built environment properties than lowland regions. It is unclear whether these environmental factors mediate/confound the association between altitude and IHD.

What this study adds
The potentially heart protective effect of living at higher altitude was only partially influenced by differences between low- and highland regions in sunshine, temperature, precipitation, topography and road density. Environmental factors appear to have an independent effect on ischemic heart disease mortality. Further analysis of the potential cumulative impact of additional modifiable environmental factors on cardiovascular health could allow to define favorable and unfavorable environments, providing a basis for tailored adaptations of the built environment with the potential to reduce associated health inequalities.

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Contributors DF conceived the study and assisted in data analysis, design of figures and tables. DF wrote the main parts of the manuscript. AS mainly performed statistical analyses, designed tables and figures and reviewed the manuscript. RP, MB and MR assisted in data analysis and interpretation, added important background knowledge and improved the manuscript by repeated readings and rephrasing as well as critical discussions of the intellectual content. All authors read and approved the final manuscript.

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Competing interest None declared.

REFERENCES

1. Sallis JF, Floyd MF, Rodríguez DA, Saelens BE. Role of built environments in physical activity, obesity, and cardiovascular disease. *Circulation* . 2012 Feb 7;125(5):729–37.

2. Schulz AJ, Kannan S, Dvonch JT, Israel BA, Allen A, James SA, et al. Social and physical environments and disparities in risk for cardiovascular disease: the healthy environments partnership conceptual model. *Environ Health Perspect*. 2005 Dec;113(12):1817–25.

3. Weinberg CR, Brown KG, Hoel DG. Altitude, radiation, and mortality from cancer and heart disease. *Radiat Res*. 1987 Nov;112(2):381–90.

4. Scarborough P, Allender S, Rayner M, Goldacre M. Contribution of climate and air pollution to variation in coronary heart disease mortality rates in England. Simpson C, editor. *PLoS One*. Public Library of Science; 2012 Jan;7(3):e32787.

5. Burtscher M. Effects of living at higher altitudes on mortality: a narrative review. *Aging Dis*. 2014 Aug;5(4):274–80.

6. Faeh D, Gutzwiller F, Bopp M. Lower mortality from coronary heart disease and stroke at higher altitudes in Switzerland. *Circulation*. 2009 Aug 11;120(6):495–501.

7. Health at a Glance 2013 . Available from: http://www.oecd.org/els/health-systems/health-at-a-glance.htm

8. Panczak R, Galobardes B, Voorpostel M, Spoerri A, Zwahlen M, Egger M. A Swiss neighbourhood index of socioeconomic position: development and association with mortality. *J Epidemiol Community Health*. 2012 Dec;66(12):1129–36.

9. Panczak R, Galobardes B, Spoerri A, Zwahlen M, Egger M. High life in the sky? Mortality by floor of residence in Switzerland. *Eur J Epidemiol*. 2013 Jun;28(6):453–62.

10. Bopp M, Spoerri A, Zwahlen M, Gutzwiller F, Paccaud F, Braun-Fahrlander C, et al. Cohort Profile: the Swiss National Cohort--a longitudinal study of 6.8 million people. *Int J Epidemiol*. 2009;38(2):379–84.

11. Spoerri A, Zwahlen M, Egger M, Bopp M. The Swiss National Cohort: a unique database for national and international researchers. *Int J Public Heal*. 2010;55(4):239–42.

12. Bopp M, Braun J, Faeh D, Gutzwiller F. Establishing a follow-up of the Swiss MONICA participants (1984-1993): record linkage with census and mortality data. *BMC Public Health*. 2010;10:562.

13. Statistik B für, editor. Bundesamt für Statistik. Eidgenössische Volkszählung 2000. Abschlussbericht zur Volkszählung 2000. Neuchâtel; 2005.

14. Pickett KE, Pearl M. Multilevel analyses of neighbourhood socioeconomic context and health outcomes: a critical review. *J Epidemiol Community Health*. 2001 Feb [cited 2015 Jul 22];55(2):111–22.

15. Faeh D, Minder C, Gutzwiller F, Bopp M. Culture, risk factors and mortality: can Switzerland add missing pieces to the European puzzle? *J Epidemiol Community Health*. 2009 Aug;63(8):639–45.

16. SwissALTI3D . Available from: http://www.swisstopo.admin.ch/internet/swisstopo/en/home/products/height/swissALTI3D.html

17. Foraster M, Deltell A, Basagaña X, Medina-Ramón M, Aguilera I, Bouso L, et al. Local determinants of road traffic noise levels versus determinants of air pollution levels in a Mediterranean city. *Environ Res*. 2011 Jan;111(1):177–83.

18. Schuler, Martin; Dessemontet PJD. Die Raumgliederung der Schweiz - Eidgenössische Volkszählung 2000. Neuchâtel; 2005.

19. MeteoSwiss data . Available from: http://www.meteoswiss.admin.ch/web/en/services/data_portal.html

20. Carroll KJ. On the use and utility of the Weibull model in the analysis of survival data. *Control Clin Trials*. 2003 Dec [cited 2015 Sep 24];24(6):682–701.

21. Harrell FE. Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis. Springer, editor. 2001.

22. Ezzati M, Horwitz MEM, Thomas DSK, Friedman AB, Roach R, Clark T, et al. Altitude, life expectancy and mortality from ischaemic heart disease, stroke, COPD and cancers: national population-based analysis of US counties. *J Epidemiol Community Health*. 2012 Jul 1;66(7):e17.

23. Voors AW, Johnson WD. Altitude and arteriosclerotic heart disease mortality in white residents of 99 of the 100 largest cities in the United States. *J Chronic Dis*. 1979 Jan;32(1-2):157–62.

24. Buechley RW, Key CR, Morris DL, Morton WE, Morgan M V. Altitude and ischemic heart disease in tricultural New Mexico: an example of confounding. *Am J Epidemiol*. 1979 Jun [cited 2014 Jun 23];109(6):663–6.

25. Baibas N, Trichopoulou A, Voridis E, Trichopoulos D. Residence in mountainous compared with lowland areas in relation to total and coronary mortality. A study in rural Greece. *J Epidemiol Community Health*. 2005 Apr;59(4):274–8.

26. Ostadal B, Kolar F. Cardiac adaptation to chronic high-altitude hypoxia: beneficial and adverse effects. *Respir Physiol Neurobiol*. 2007 Sep 30;158(2-3):224–36.

27. Bärtsch P, Saltin B. General introduction to altitude adaptation and mountain sickness. *Scand J Med Sci Sports*. 2008 Aug;18 Suppl 1:1–10. 7

28. Stembridge M, Ainslie PN, Hughes MG, Stöhr EJ, Cotter JD, Nio AQX, et al. Ventricular structure, function and mechanics at high altitude: chronic remodelling in Sherpa verses short-term lowlander adaptation. *J Appl Physiol*. 2014 May 29

29. Lewis NCS, Bailey DM, Dumanoir GR, Messinger L, Lucas SJE, Cotter JD, et al. Conduit artery structure and function in lowlanders and native highlanders: relationships with oxidative stress and role of sympathoexcitation. *J Physiol*. 2014 Mar 1;592(Pt 5):1009–24.

30. Passino C, Bernardi L, Spadacini G, Calciati A, Robergs R, Anand I, et al. Autonomic regulation of heart rate and peripheral circulation: comparison of high altitude and sea level residents. *Clin Sci (Lond)*. 1996 Jan;91 Suppl:81–3.

31. Hurtado A, Escudero E, Pando J, Sharma S, Johnson RJ. Cardiovascular and renal effects of chronic exposure to high altitude. *Nephrol Dial Transplant*. 2012 Dec 1;27 Suppl 4(suppl_4):iv11–6.

32. Essop MF. Cardiac metabolic adaptations in response to chronic hypoxia. *J Physiol*. 2007 Nov 1;584(Pt 3):715–26.

33. Sasaki H, Fukuda S, Otani H, Zhu L, Yamaura G, Engelman RM, et al. Hypoxic preconditioning triggers myocardial angiogenesis: a novel approach to enhance contractile functional reserve in rat with myocardial infarction. *J Mol Cell Cardiol.* 2002 Mar;34(3):335–48.

34. Koller EA, Lesniewska B, Bührer A, Bub A, Kohl J. The effects of acute altitude exposure in Swiss highlanders and lowlanders. *Eur J Appl Physiol Occup Physiol*. 1993 Jan;66(2):146–54.

35. Tin'kov AN, Aksenov VA. Effects of intermittent hypobaric hypoxia on blood lipid concentrations in male coronary heart disease patients. *High Alt Med Biol.* Mary Ann Liebert, Inc.; 2002 Jan 6;3(3):277–82.

36. Fiori G, Facchini F, Pettener D, Rimondi A, Battistini N, Bedogni G. Relationships between blood pressure, anthropometric characteristics and blood lipids in high- and low-altitude populations from Central Asia. *Ann Hum Biol.* Jan;27(1):19–28.

37. Yi X, Liang Y, Huerta-Sanchez E, Jin X, Cuo ZXP, Pool JE, et al. Sequencing of 50 human exomes reveals adaptation to high altitude. *Science*. 2010 Jul 2;329(5987):75–8.

38. Faeh D, Braun J, Bopp M. Prevalence of obesity in Switzerland 1992-2007: the impact of education, income and occupational class. *Obes Rev*. 2011 Mar;12(3):151–66.

39. Maag J, Braun J, Bopp M, Faeh D. Direct estimation of death attributable to smoking in Switzerland based on record linkage of routine and observational data. *Nicotine Tob Res*. 2013 Oct;15(9):1588–97.

FIGURES

Figure 1 Altitudinal ranges (A), terrain slope (%, B), residential buildings (C), mean annual (1981-85) sunshine duration (% of maximum, D), temperature (°C, E) and precipitation (mm, F) in Switzerland

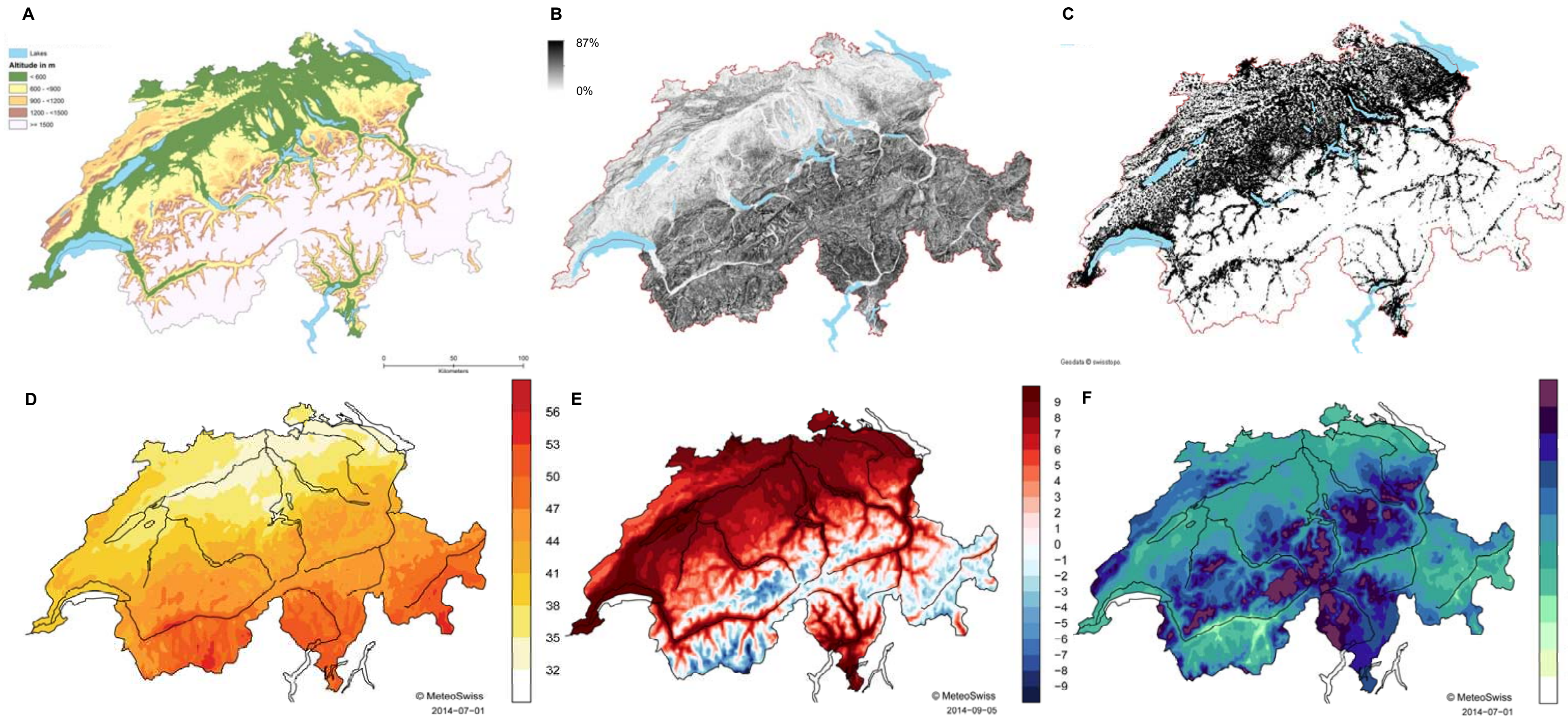
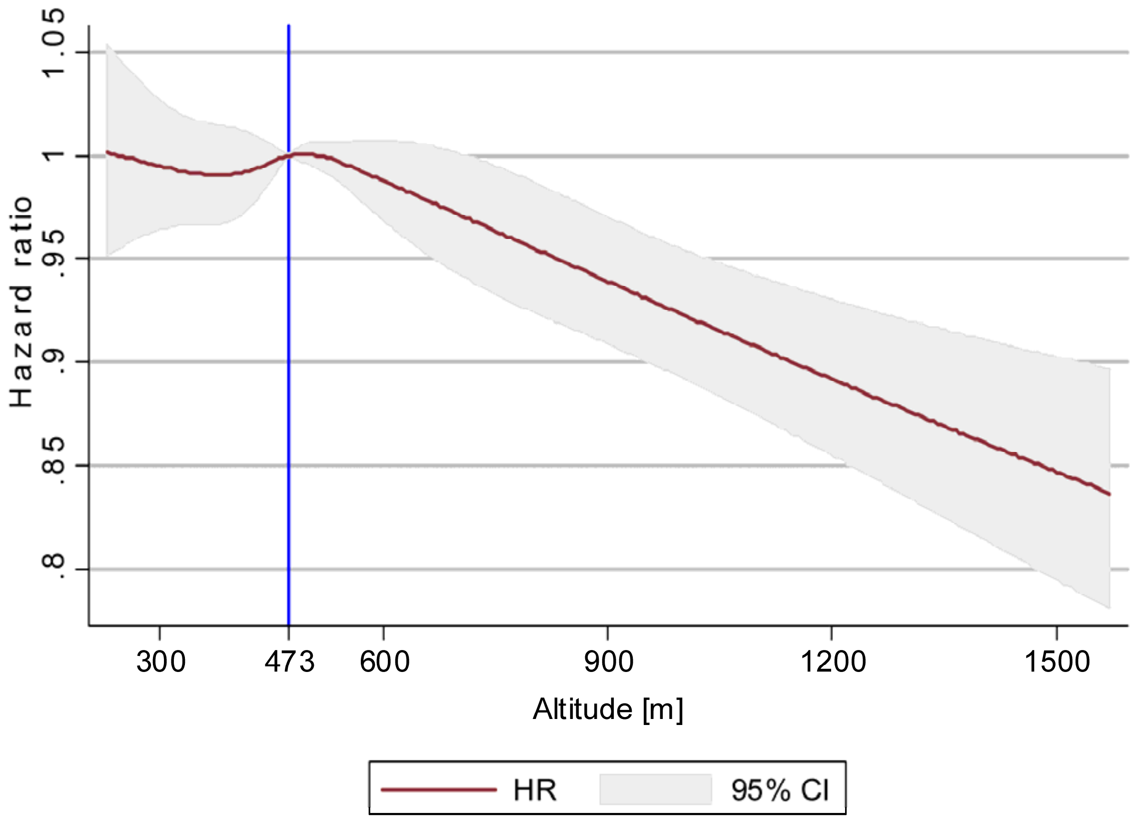


Figure 2 Hazard ratios (HR) with 95% confidence interval (CI) for ischemic heart disease mortality by altitude for percentiles 0.1 to 99.9 (altitude range 199-1804m) of the study population (aged 40-84 years), Swiss National Cohort 2000-2008*



*cubic splines with median altitude (473m) as reference to report HRs, adjusted for age, sex, marital status, education, profession, type of household, language region, urbanisation, Swiss SEP, sunshine duration, precipitation, temperature, slope and distance to main roads

ELECTRONIC SUPPLEMENTARY MATERIAL (3 Figures, 6 Tables)

Figures

Figure A1 Density of the population in Switzerland

Figure A2 Main road network in Switzerland

Figure A3 Hazard ratios (HR) with 95% confidence interval (CI) for ischemic heart mortality by altitude (full range of altitude, 195-2971m)

Tables

Table A1 Correlation between environmental variables, Swiss National Cohort 2000-2008

Table A2 Continuation of Table 1: Number and percentage of Swiss residents by socio-economic/demographic factors, distributed over five altitudinal ranges, Swiss National Cohort 2000-2008

Table A3 Continuation of Table 2: Hazard ratios of Swiss residents living at five altitudinal ranges from models with increasing adjustment, socio-economic/demographic factors, Swiss National Cohort 2000-2008

Table A4 Hazard ratios for ischemic heart disease mortality of Swiss residents living below 600m (N=3,321,321), Swiss National Cohort 2000-2008

Table A5 Hazard ratios for ischemic heart disease mortality of Swiss residents living in the mountain area (N= 1,159,173), Swiss National Cohort 2000-2008

Table A6 Hazard ratios for ischemic heart disease mortality of Swiss residents including changes in altitude between place of birth and residence at census (N= 2,953,959*), Swiss National Cohort 2000-2008

Figures

Figure A1 Density of the population in Switzerland

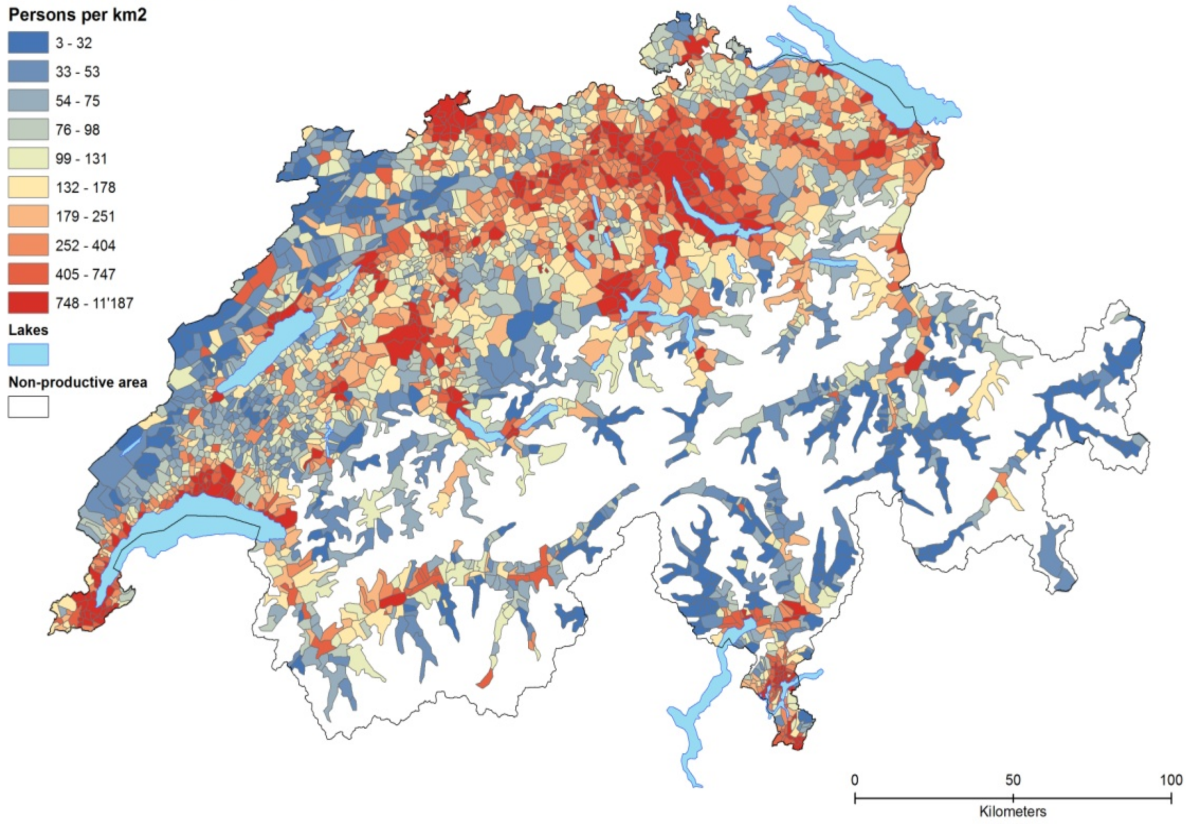


Figure A2 Main road network in Switzerland

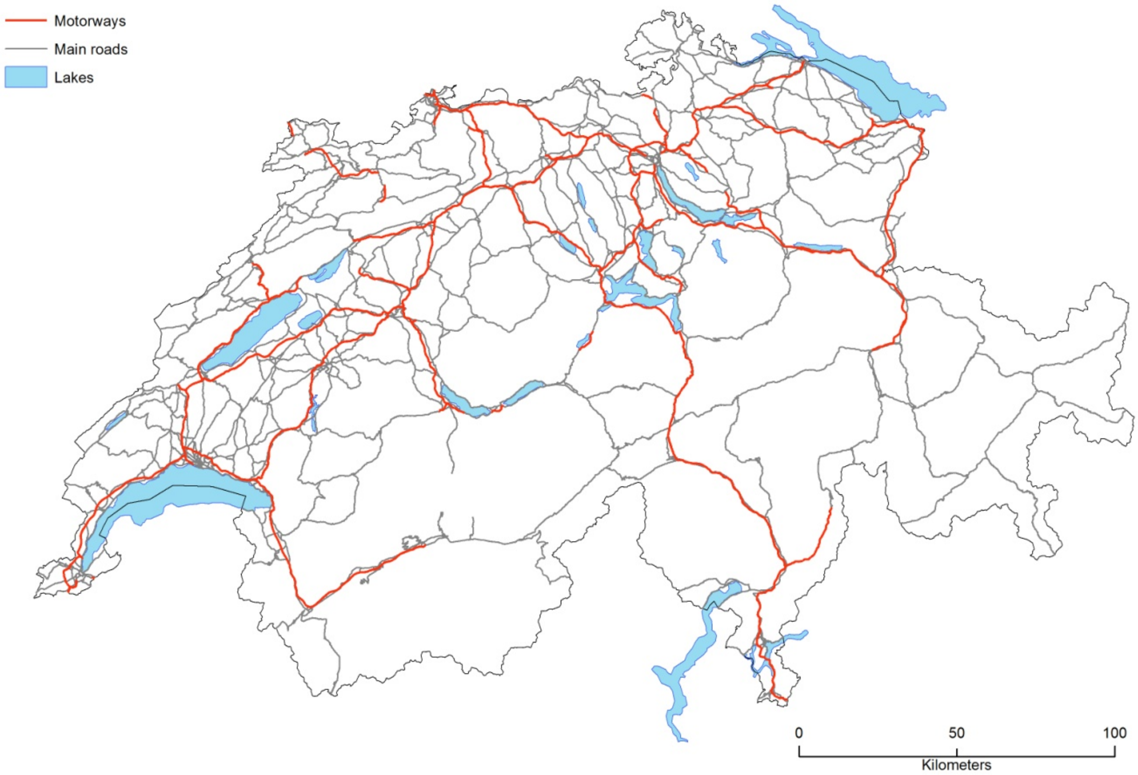
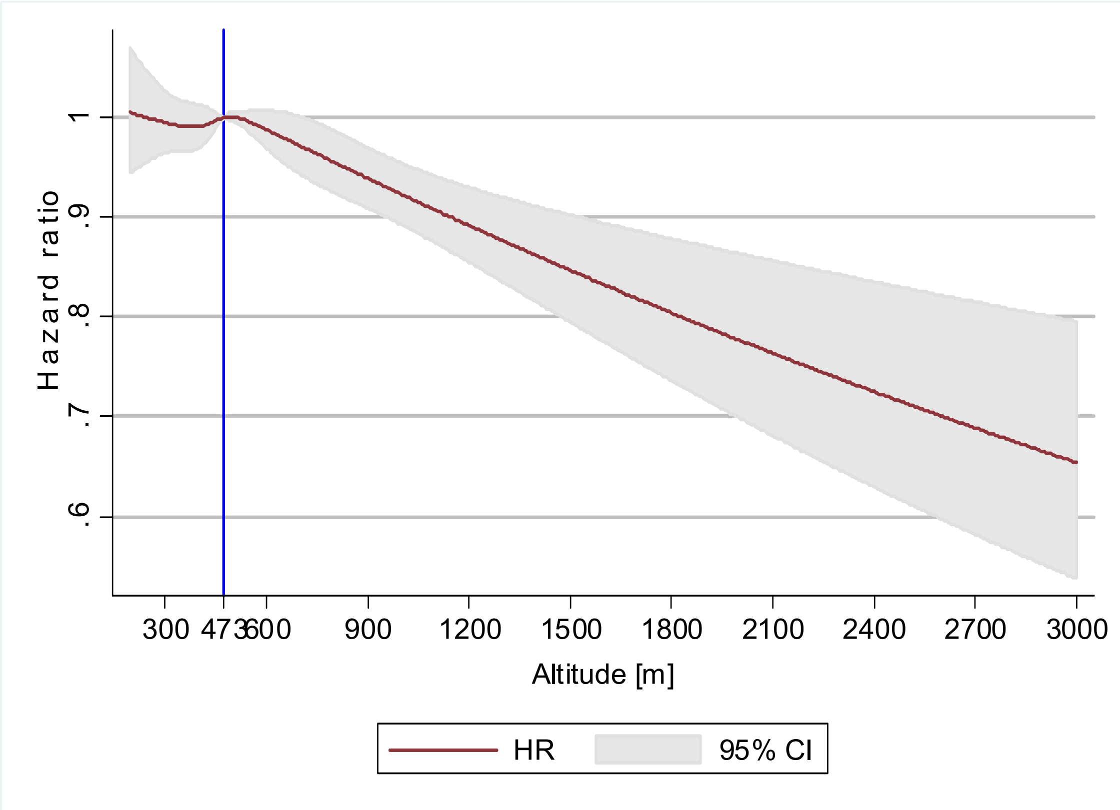


Figure A3 Hazard ratios (HR) with 95% confidence interval (CI) for ischemic heart mortality by altitude (full range of altitude, 195-2971m)



*cubic splines with median altitude (473m) as reference to report HRs, adjusted for age, sex, marital status, education, profession, type of household, language region, urbanization, Swiss SEP, sunshine duration, precipitation, temperature, slope and distance to main roads

Tables

Table A1 Correlation between environmental variables, Swiss National Cohort 2000-2008

	Altitude	Sunshine	Precipitation	Temperature	Slope	Road distance
Altitude	1					
Sunshine	0,30	1				
Precipitation	0,19	0,28	1			
Temperature	-0,83	-0,09	-0,11	1		
Slope	0,23	0,16	0,16	-0,15	1	
Road distance[a]	0,38	0,18	0,08	-0,35	0,13	1

[a] Distance to main roads in meter as a proxy for noise and air pollution

Table A2 Continuation of Table 1: Number and percentage of Swiss residents by socio-economic/demographic factors, distributed over five altitudinal ranges, Swiss National Cohort 2000-2008

Altitude at 2000 census	<600		600 - <900		900 - <1200		1200 - <1500		>=1500		Total	
in [m] above sea level	N	%	N	%	N	%	N	%	N	%	N	%
Marital status												
Single	439 206	13	71 720	12	16 115	12	5 635	13	4 299	15	536 975	13
Married	2 327 096	70	461 244	74	102 042	73	31 982	73	21 304	72	2 943 668	71
Widowed	242 965	7	46 840	8	11 992	9	3 581	8	1 916	7	307 294	7
Divorced	312 054	9	44 715	7	9 653	7	2 363	5	1 998	7	370 783	9
Education												
Primary	1 140 472	34	232 618	37	63 708	46	20 042	46	10 743	36	1 467 583	35
Secondary	1 521 150	46	282 049	45	58 870	42	18 333	42	14 162	48	1 894 564	46
Tertiary	659 699	20	109 852	18	17 224	12	5 186	12	4 612	16	796 573	19
Professional attainment												
Management	85 820	3	13 854	2	1 951	1	565	1	620	2	102 810	3
Self-employed	213 419	6	53 734	9	14 204	10	4 728	11	3 241	11	289 326	7
Professionals	205 311	6	32 550	5	4 360	3	1 258	3	1 361	5	244 840	6
Skilled labour	862 677	26	157 475	25	30 052	22	8 770	20	7 274	25	1 066 248	26
Unskilled labour	218 835	7	39 472	6	9 711	7	2 898	7	2 447	8	273 363	7
Not classified	469 410	14	92 140	15	21 579	15	7 370	17	5 019	17	595 518	14
Unemployed	79 252	2	10 353	2	1 849	1	484	1	308	1	92 246	2
Not in paid empl.	1 186 597	36	224 941	36	56 096	40	17 488	40	9 247	31	1 494 369	36
Type of houshold												
Single	670 698	20	98 064	16	24 755	18	7 688	18	6 037	21	807 242	19
Multi person	2 618 236	79	520 066	83	113 652	81	35 377	81	22 328	76	3 309 659	80
Institution	32 387	1	6 389	1	1 395	1	496	1	1 152	4	41 819	1
Language region												
German	2 468 973	74	416 832	67	64 782	46	28 654	66	26 306	89	3 005 547	72
French	673 852	20	196 000	31	68 706	49	14 164	33	2 840	10	955 562	23
Italian	178 496	5	11 687	2	6 314	5	743	2	371	1	197 611	5
Swiss-SEP index deciles												
Dec1 - low	325 223	10	106 234	17	44 691	32	15 289	35	6 566	22	498 003	12
Dec2	312 830	9	92 877	15	30 200	22	9 335	21	3 987	14	449 229	11
Dec3	315 163	10	77 205	12	21 056	15	6 093	14	2 968	10	422 485	10
Dec4	322 512	10	67 907	11	15 469	11	4 431	10	3 188	11	413 507	10
Dec5	330 018	10	59 925	10	11 217	8	3 871	9	3 356	11	408 387	10
Dec6	341 319	10	51 593	8	7 672	6	1 998	5	3 215	11	405 797	10
Dec7	347 636	11	46 182	7	5 036	4	1 482	3	2 777	9	403 113	10
Dec8	349 371	11	44 612	7	3 064	2	655	2	2 426	8	400 128	10
Dec9	345 005	10	42 680	7	1 222	1	328	1	933	3	390 168	9
Dec10 - high	332 244	10	35 304	6	175	0	79	0	101	0	367 903	9

Table A3 Continuation of Table 2: Hazard ratios of Swiss residents living at five altitudinal ranges from models with increasing adjustment, socio-economic/demographic factors, Swiss National Cohort 2000-2008

	Crude Model[a]	**Model 1**[b]	**Model 2**[c]	**Model 3**[c]	**Model 4**[c]	**Model 5**[c]	**Model 6**[c]	**Model 7**[c]
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Altitude at census 2000 [m above sea level]								
<600m	1	1	1	1	1	1	1	1
600-<900m	1.01 (0.99-1.03)	0.98 (0.95-1.00)	0.97 (0.94-0.99)	0.98 (0.96-1.00)	0.98 (0.96-1.00)	0.98 (0.96-1.00)	0.97 (0.95-1.00)	0.97 (0.94-1.00)
900-<1200m	0.96 (0.93-1.00)	0.96 (0.92-1.00)	0.96 (0.92-1.01)	0.97 (0.93-1.01)	0.96 (0.92-1.00)	0.96 (0.93-1.00)	0.97 (0.93-1.02)	0.96 (0.92-1.01)
1200-<1500m	0.85 (0.80-0.92)	0.78 (0.72-0.83)	0.82 (0.76-0.88)	0.79 (0.73-0.85)	0.78 (0.72-0.84)	0.78 (0.72-0.84)	0.83 (0.77-0.90)	0.82 (0.76-0.89)
>=1500m	0.75 (0.68-0.83)	0.67 (0.60-0.74)	0.73 (0.65-0.81)	0.68 (0.61-0.75)	0.67 (0.60-0.74)	0.67 (0.60-0.74)	0.74 (0.66-0.82)	0.73 (0.65-0.81)
Gender								
Men	1	1	1	1	1	1	1	1
Women	0.45 (0.44-0.46)	0.37 (0.36-0.38)	0.37 (0.36-0.38)	0.37 (0.36-0.38)	0.37 (0.36-0.38)	0.37 (0.36-0.38)	0.37 (0.36-0.38)	0.37 (0.36-0.38)
Marital status								
Single	1.11 (1.08-1.14)	1.27 (1.23-1.31)	1.27 (1.23-1.31)	1.27 (1.23-1.31)	1.27 (1.23-1.31)	1.27 (1.23-1.31)	1.27 (1.23-1.31)	1.27 (1.23-1.31)
Married	1	1	1	1	1	1	1	1
Widowed	0.98 (0.96-0.99)	1.38 (1.34-1.41)	1.37 (1.34-1.41)	1.38 (1.34-1.41)	1.38 (1.34-1.41)	1.38 (1.34-1.41)	1.37 (1.34-1.41)	1.37 (1.34-1.41)
Divorced	1.17 (1.14-1.20)	1.39 (1.35-1.44)	1.39 (1.35-1.44)	1.39 (1.35-1.44)	1.39 (1.35-1.44)	1.39 (1.35-1.44)	1.39 (1.35-1.44)	1.39 (1.35-1.44)
Education								
Primary	1.08 (1.06-1.11)	1.36 (1.32-1.39)	1.35 (1.32-1.39)	1.35 (1.32-1.39)	1.36 (1.32-1.39)	1.36 (1.32-1.39)	1.35 (1.32-1.39)	1.35 (1.32-1.39)
Secondary	1.06 (1.03-1.09)	1.18 (1.15-1.21)	1.18 (1.15-1.21)	1.18 (1.15-1.21)	1.18 (1.15-1.21)	1.18 (1.15-1.21)	1.18 (1.15-1.21)	1.18 (1.15-1.21)
Tertiary	1	1	1	1	1	1	1	1
Professional attainment								
Management	0.92 (0.83-1.02)	0.94 (0.84-1.04)	0.94 (0.84-1.04)	0.94 (0.85-1.04)	0.94 (0.84-1.04)	0.94 (0.84-1.04)	0.94 (0.85-1.04)	0.94 (0.84-1.04)
Self-employed	1.28 (1.20-1.36)	1.17 (1.10-1.24)	1.17 (1.10-1.24)	1.17 (1.10-1.24)	1.17 (1.10-1.24)	1.17 (1.10-1.24)	1.17 (1.10-1.24)	1.17 (1.10-1.24)
Professionals	0.88 (0.81-0.95)	0.88 (0.81-0.96)	0.88 (0.81-0.96)	0.88 (0.81-0.96)	0.88 (0.81-0.96)	0.88 (0.81-0.96)	0.88 (0.81-0.96)	0.88 (0.81-0.96)
Skilled labour	1	1	1	1	1	1	1	1
Unskilled labour	1.02 (0.95-1.10)	0.98 (0.91-1.06)	0.98 (0.91-1.06)	0.98 (0.91-1.06)	0.98 (0.91-1.06)	0.98 (0.91-1.06)	0.98 (0.91-1.06)	0.98 (0.91-1.06)
Not classified	1.28 (1.22-1.34)	1.32 (1.26-1.39)	1.32 (1.26-1.39)	1.32 (1.26-1.39)	1.32 (1.26-1.39)	1.32 (1.25-1.38)	1.32 (1.26-1.39)	1.32 (1.26-1.39)
Unemployed	1.78 (1.63-1.95)	1.81 (1.66-1.98)	1.82 (1.66-1.99)	1.81 (1.66-1.98)	1.81 (1.66-1.98)	1.80 (1.65-1.97)	1.81 (1.65-1.98)	1.81 (1.65-1.98)
Not in paid empl.	1.26 (1.20-1.31)	1.56 (1.49-1.63)	1.56 (1.49-1.64)	1.56 (1.49-1.63)	1.56 (1.49-1.63)	1.56 (1.49-1.63)	1.56 (1.49-1.64)	1.56 (1.49-1.64)
Type of household								
Single	0.98 (0.96-0.99)	1.03 (1.00-1.05)	1.03 (1.00-1.05)	1.03 (1.00-1.05)	1.03 (1.00-1.05)	1.03 (1.00-1.05)	1.03 (1.00-1.05)	1.03 (1.00-1.05)
Multi person	1	1	1	1	1	1	1	1
Institution	1.64 (1.57-1.70)	1.58 (1.52-1.65)	1.58 (1.52-1.65)	1.58 (1.52-1.65)	1.58 (1.52-1.65)	1.58 (1.52-1.65)	1.58 (1.52-1.65)	1.58 (1.52-1.65)
Language region								
German	1	1	1	1	1	1	1	1
French	0.67 (0.66-0.69)	0.65 (0.64-0.67)	0.70 (0.68-0.71)	0.65 (0.64-0.67)	0.65 (0.64-0.66)	0.65 (0.64-0.66)	0.70 (0.68-0.71)	0.69 (0.68-0.71)

Italian	0.85 (0.83-0.88)	0.81 (0.78-0.84)	0.85 (0.81-0.90)	0.82 (0.79-0.84)	0.81 (0.78-0.84)	0.81 (0.78-0.84)	0.86 (0.82-0.90)	0.86 (0.82-0.90)
Urbanization								
Urban	1	1	1	1	1	1	1	1
Peri-urban	1.01 (1.00-1.03)	0.99 (0.98-1.01)	0.99 (0.97-1.00)	1.00 (0.98-1.01)	0.99 (0.98-1.01)	1.00 (0.98-1.02)	0.99 (0.98-1.01)	0.99 (0.97-1.01)
Rural	1.11 (1.09-1.13)	1.00 (0.98-1.02)	0.99 (0.96-1.01)	1.01 (0.99-1.03)	1.00 (0.98-1.02)	1.01 (0.99-1.03)	1.00 (0.97-1.02)	0.99 (0.97-1.02)
Swiss-SEP index deciles								
Dec1 - low	1	1	1	1	1	1	1	1
Dec2	0.97 (0.94-1.00)	0.96 (0.93-0.99)	0.96 (0.93-0.99)	0.96 (0.93-0.99)	0.96 (0.93-0.99)	0.96 (0.93-0.99)	0.96 (0.93-0.99)	0.96 (0.93-0.99)
Dec3	0.98 (0.95-1.01)	0.96 (0.93-0.98)	0.96 (0.93-0.98)	0.96 (0.93-0.99)	0.96 (0.93-0.98)	0.96 (0.93-0.99)	0.96 (0.93-0.99)	0.96 (0.93-0.99)
Dec4	0.97 (0.95-1.00)	0.95 (0.92-0.98)	0.95 (0.92-0.98)	0.95 (0.92-0.98)	0.95 (0.92-0.98)	0.95 (0.92-0.98)	0.95 (0.92-0.98)	0.95 (0.92-0.98)
Dec5	0.94 (0.92-0.97)	0.92 (0.89-0.94)	0.91 (0.89-0.94)	0.92 (0.89-0.94)	0.92 (0.89-0.94)	0.92 (0.89-0.95)	0.92 (0.89-0.95)	0.92 (0.89-0.95)
Dec6	0.93 (0.91-0.96)	0.91 (0.88-0.94)	0.91 (0.88-0.94)	0.91 (0.89-0.94)	0.91 (0.88-0.94)	0.92 (0.89-0.95)	0.92 (0.89-0.95)	0.92 (0.89-0.95)
Dec7	0.91 (0.88-0.93)	0.89 (0.86-0.92)	0.89 (0.86-0.92)	0.89 (0.86-0.92)	0.89 (0.86-0.92)	0.90 (0.87-0.92)	0.90 (0.87-0.93)	0.89 (0.87-0.92)
Dec8	0.85 (0.83-0.88)	0.85 (0.82-0.88)	0.84 (0.82-0.87)	0.85 (0.82-0.88)	0.85 (0.82-0.88)	0.85 (0.83-0.88)	0.86 (0.83-0.88)	0.85 (0.83-0.88)
Dec9	0.81 (0.78-0.84)	0.81 (0.79-0.84)	0.81 (0.78-0.84)	0.82 (0.79-0.85)	0.82 (0.79-0.84)	0.82 (0.80-0.85)	0.83 (0.80-0.85)	0.82 (0.79-0.85)
Dec10 - high	0.72 (0.70-0.75)	0.74 (0.71-0.77)	0.73 (0.71-0.76)	0.74 (0.72-0.77)	0.74 (0.71-0.77)	0.75 (0.72-0.78)	0.75 (0.72-0.78)	0.75 (0.72-0.78)

[a]each variable adjusted for age
[b]adjusted for age, sex, marital status, education, profession, type of household, language region, urbanization and Swiss SEP
[c]adjusted for age, sex, marital status, education, profession, type of household, language region, urbanization, Swiss SEP and variables listed in respective column of Table 2

Table A4 Hazard ratios for ischemic heart disease mortality of Swiss residents living below 600m (N=3,321,321), Swiss National Cohort 2000-2008

	Crude Model[a] HR (95% CI)	Full Model[b] HR (95% CI)
Sunshine duration, % of max		
32.6 - <35.0%	1	1
35.0 - <35.8%	1.02 (1.00-1.04)	1.05 (1.02-1.07)
35.8 - <37.6%	0.95 (0.93-0.98)	1.02 (1.00-1.05)
37.6 - <41.4%	0.72 (0.70-0.74)	0.96 (0.93-0.99)
41.4 - 58.5%	0.84 (0.82-0.87)	0.98 (0.95-1.02)
Precipitation [mm]		
540 - 993	1	1
994 - 1080	1.09 (1.07-1.12)	1.04 (1.01-1.06)
1081 - 1165	1.13 (1.11-1.16)	1.07 (1.04-1.09)
1166 - 1316	1.12 (1.09-1.15)	1.05 (1.02-1.08)
1317 - 2735	1.10 (1.07-1.13)	1.07 (1.04-1.11)
Temperature [degree C]		
-3.3-<8.6	1	1
8.6-<9.2	1.00 (0.96-1.03)	1.02 (0.98-1.06)
9.2-<9.6	1.02 (0.98-1.05)	1.05 (1.01-1.09)
9.6-<10.0	0.96 (0.93-1.00)	1.00 (0.97-1.04)
10.0-<13.4	0.75 (0.72-0.78)	1.00 (0.96-1.04)
Slope at place of residence		
0 - <3%	1	1
3 - <5%	1.00 (0.98-1.02)	1.01 (0.98-1.03)
5 - <10%	0.98 (0.96-1.00)	0.99 (0.97-1.01)
10 - <15%	0.91 (0.88-0.94)	0.94 (0.92-0.97)
15 - <25%	0.93 (0.89-0.97)	0.98 (0.94-1.03)
>=25%	0.84 (0.77-0.92)	0.93 (0.84-1.01)
Distance to main road		
0 - <50m	1	1
50 - <100m	0.96 (0.93-0.99)	0.97 (0.94-1.00)
100 - <150m	0.93 (0.90-0.96)	0.94 (0.91-0.98)
150 - <200m	0.92 (0.88-0.95)	0.94 (0.91-0.97)
>=200m	0.93 (0.91-0.95)	0.92 (0.90-0.95)

[a] adjusted for age
[b] adjusted for age, gender, marital status, education, profession, type of household, language region, urbanization, Swiss SEP and variables listed in table

Table A5 Hazard ratios for ischemic heart disease mortality of Swiss residents living in the mountain area (N= 1,159,173), Swiss National Cohort 2000-2008

	Crude Model[a] HR (95% CI)	Full Model[b] HR (95% CI)
Altitude at census 2000		
<600m	1	1
600-<900m	1.05 (1.01-1.08)	0.94 (0.90-0.98)
900-<1200m	1.01 (0.97-1.06)	0.94 (0.88-1.00)
1200-<1500m	0.84 (0.78-0.90)	0.81 (0.75-0.88)
>=1500m	0.73 (0.66-0.81)	0.72 (0.64-0.81)
Sunshine duration, % of max		
32.6 - <35.0%	1	1
35.0 - <35.8%	1.12 (1.05-1.20)	1.01 (0.94-1.08)
35.8 - <37.6%	1.06 (1.00-1.12)	0.96 (0.90-1.02)
37.6 - <41.4%	1.10 (1.05-1.16)	1.02 (0.96-1.08)
41.4 - 58.5%	0.89 (0.86-0.93)	0.93 (0.88-0.98)
Precipitation [mm]		
540 - 993	1	1
994 - 1080	1.11 (1.05-1.17)	0.99 (0.94-1.05)
1081 - 1165	1.26 (1.19-1.34)	1.06 (1.00-1.13)
1166 - 1316	1.21 (1.15-1.27)	1.03 (0.98-1.09)
1317 - 2735	1.18 (1.13-1.23)	1.06 (1.01-1.11)
Temperature [degree C]		
-3.3-<8.6	1	1
8.6-<9.2	0.98 (0.94-1.02)	0.99 (0.94-1.04)
9.2-<9.6	0.98 (0.94-1.02)	1.00 (0.95-1.05)
9.6-<10.0	0.98 (0.95-1.02)	1.00 (0.95-1.05)
10.0-<13.4	0.91 (0.87-0.94)	1.03 (0.96-1.11)
Slope at place of residence		
0 - <3%	1	1
3 - <5%	0.98 (0.94-1.02)	0.98 (0.94-1.02)
5 - <10%	0.98 (0.95-1.01)	0.99 (0.96-1.03)
10 - <15%	0.95 (0.91-0.99)	0.99 (0.95-1.03)
15 - <25%	0.89 (0.85-0.94)	0.96 (0.91-1.01)
>=25%	0.83 (0.76-0.91)	0.92 (0.84-1.01)
Distance to main road		
0 - <50m	1	1
50 - <100m	0.93 (0.88-0.98)	0.93 (0.88-0.99)
100 - <150m	0.92 (0.87-0.97)	0.92 (0.87-0.98)
150 - <200m	0.86 (0.81-0.91)	0.88 (0.82-0.93)
>=200m	0.91 (0.88-0.95)	0.91 (0.87-0.95)

[a] adjusted for age
[b] adjusted for age, gender, marital status, education, profession, type of household, language region, urbanization, Swiss SEP and variables listed in table

Table A6 Hazard ratios for ischemic heart disease mortality of Swiss residents including changes in altitude between place of birth and residence at census (N= 2,953,959*), Swiss National Cohort 2000-2008

	Crude Model[a] HR (95% CI)	Full Model[b] HR (95% CI)
Altitude range in m above sea level (census 2000)		
<600		1
600-<900		0.96 (0.93-0.99)
900-<1200		0.96 (0.91-1.01)
1200-<1500		0.85 (0.78-0.92)
≥1500		0.75 (0.66-0.85)
Change in altitude (place of birth vs census)		
Moved down >400m	0.89 (0.86-0.93)	0.94 (0.91-0.98)
Stayed within +-400m	1	1
Moved up >400m	0.85 (0.80-0.90)	1.01 (0.94-1.08)
Mean annual sunshine duration in % of maximum		
32.6 - <35.0		1
35.0 - <35.8		1.05 (1.02-1.08)
35.8 - <37.6		1.01 (0.98-1.04)
37.6 - <41.4		0.95 (0.92-0.98)
41.4 - 58.5		0.94 (0.91-0.97)
Mean annual precipitation in mm		
540 - 993		1
994 - 1080		1.02 (1.00-1.05)
1081 - 1165		1.06 (1.03-1.09)
1166 - 1316		1.04 (1.01-1.07)
1317 - 2735		1.09 (1.06-1.13)
Mean annual temperature in degree C		
-3.3-<8.6		1
8.6-<9.2		1.01 (0.97-1.04)
9.2-<9.6		1.03 (0.99-1.06)
9.6-<10.0		0.99 (0.95-1.02)
10.0-<13.4		0.98 (0.94-1.02)
Slope at place of residence in %		
0 - <3 (flat)		1
3 - <5		0.98 (0.96-1.01)
5 - <10		0.98 (0.96-1.00)
10 - <15		0.95 (0.93-0.98)
15 - <25		0.95 (0.92-0.99)
≥25		0.93 (0.85-1.01)
Distance to main road in m		
0 - <50		1
50 - <100		0.96 (0.93-1.00)
100 - <150		0.93 (0.90-0.96)
150 - <200		0.91 (0.88-0.95)
≥200		0.91 (0.89-0.93)

[a] adjusted for age
[b] adjusted for age, gender, marital status, education, profession, type of household, language region, urbanization, Swiss SEP and variables listed in table
* 1,204,764 persons did not have the information on the place of birth and were excluded